BMJ

BMJ 2014;348:g2547 doi: 10.1136/bmj.g2547 (Published 10 April 2014)

RESEARCH

Zanamivir for influenza in adults and children: systematic review of clinical study reports and summary of regulatory comments

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Abstract

Objectives To describe the potential benefits and harms of zanamivir.

Design Systematic review of clinical study reports of randomised placebo controlled trials and regulatory information

Data sources Clinical study reports, trial registries, electronic databases, regulatory archives, and correspondence with manufacturers.

Eligibility criteria for selecting studies Randomised placebo controlled trials in adults and children who had confirmed or suspected exposure to natural influenza.

Main outcome measures Time to first alleviation of symptoms, influenza outcomes and complications, admissions to hospital, and adverse events in the intention to treat (ITT) population.

Results We included 28 trials in stage 1 (judgment of appropriate study design) and 26 in stage 2 (formal analysis). For treatment of adults, zanamivir reduced the time to first alleviation of symptoms of influenza-like illness by 0.60 days (95% confidence interval 0.39 to 0.81, P<0.001, I^2=9%), which equates to an average 14.4 hours' reduction, or a 10% reduction in mean duration of symptoms from 6.6 days to 6.0 days. Time to first alleviation of symptoms was shorter in all participants when any relief drugs were allowed compared with no use. Zanamivir did not reduce the risk of self reported investigator mediated pneumonia (risk difference 0.17%, −0.73% to 0.70%) or radiologically confirmed pneumonia (−0.06%, −6.56% to 2.11%) in adults. The effect on pneumonia in children was also not significant (0.56%, −1.64% to 1.04%). There was no significant effect on otitis media or sinusitis in both adults and children, with only a small effect noted for bronchitis in adults (1.80%, 0.65% to 2.80%), but not in children. There were no data to assess effects on admissions in adults and children. Zanamivir tended to be well tolerated. In zanamivir prophylaxis studies, symptomatic influenza in individuals was significantly reduced (1.98%, (0.98% to 2.54%); reducing event rates from 3.26% to 1.27%, which means 51 people need to be treated to prevent one influenza case (95% confidence interval, 40 to 103). In contrast, the prophylaxis effect on asymptomatic influenza cases was not significant in individuals (risk difference 0.14%, −1.10% to 1.10%) or in households (1.32%, −2.20% to 3.84%). In households treated prophylactically there was an effect on symptomatic influenza (14.84%, 12.18% to 16.55%), but this was based on only two small studies including 824 participants. Prophylaxis in adults reduced unverified pneumonia (0.32%, 0.09% to 0.41%; NNTB (number needed to treat to benefit) 311, 244 to 1086) but had no effect on pneumonia in children or on bronchitis or sinusitis in adults or children (risk difference 0.32%, 0.09% to 0.41%; NNTB 311, 244 to 1086).

Conclusions Based on a full assessment of all trials conducted, zanamivir reduces the time to symptomatic improvement in adults (but

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Appendix 1: Search methods for identification of clinical study reports of zanamivir
Appendix 2: Searches for regulatory information
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Appendix 4: List of protocol amendments in zanamivir prophylaxis trials
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not in children) with influenza-like illness by just over half a day, although this effect might be attenuated by symptom relief medication. Zanamivir also reduces the proportion of patients with laboratory confirmed symptomatic influenza. We found no evidence that zanamivir reduces the risk of complications of influenza, particularly pneumonia, or the risk of hospital admission or death. Its harmful effects were minor (except for bronchospasm), perhaps because of low bioavailability.

Introduction

Zanamivir was the first neuraminidase inhibitor approved for the prevention and treatment of influenza. It is administered as an inhaled powder for use in adults and children aged over 7. Previous systematic reviews concluded that zanamivir was effective for the prophylaxis of symptomatic influenza-like illness and also provided symptomatic relief in influenza-like illness, with no evidence of reduction in complications.[1] In children, zanamivir seemed to have modest benefits in reducing duration of illness with influenza.[2]

However, these conclusions have been undermined by publication bias, missing data, limitations in the design of the studies, and the conduct and reporting of trials.[1 2] To deal with these problems, and to update our last review published in January 2012,[3] we requested all relevant clinical study reports from the manufacturer, GSK.[4] Clinical study reports (CSRs) are documents reporting on clinical trials performed by drug manufacturers. They are typically extensive, comprising protocols, methods, and results for each trial. These reports are provided by manufacturers to drug regulators for a drug to be considered for market approval and are otherwise unpublished.

On 14 February 2013, GSK, the manufacturer of zanamivir (Relenza), delivered the first of several DVDs containing redacted clinical study reports. Delivery was complete by the late summer.[4] This amounted to 266 files containing 16 347 pages on 28 trials. This contrasts markedly with the evidence base included in previous reviews and used for decision making. For example, only 10 trials were included in a 2002 Heath Technology Assessment (HTA) review that underpinned early cost effectiveness, and in 2009 the National Institute for Health and Care Excellence (NICE) identified and included only 13 trials in their review of zanamivir.[5] Establishment of clinical recommendations based on less than half of the evidence is clearly inadequate. For the first time, our systematic review on zanamivir presents results using full clinical study reports obtained without the need for a contract or as a result of litigation and no need to access a controlled environment such as a company website.

Methods

Search strategy

The protocol was as reported in the corresponding Cochrane review[6] with amendments published in 2012 and 2013. We used various methods applied to a range of sources (open literature, manufacturers, and regulatory bodies) to identify clinical trials funder by manufacturers and other sources. The methods, as well as our methods for obtaining relevant clinical study reports, are detailed in appendices 1 and 2. We updated our searches of the electronic databases of published studies previously carried out for the Cochrane reviews on neuraminidase inhibitors in children[7] and healthy adults[8] and then updated the searches again on the 22 July 2013. Our detailed correspondence with GSK is available online at the BMJ open data campaign at www.bmj.com/open-data/relenza.

Selection of studies

We included randomised controlled trials testing the effects of zanamivir for prophylaxis, postexposure prophylaxis (PEP), and treatment of influenza. Because of discrepancies between published and unpublished reports of the same trials, we decided to include only those trials for which we had unabridged clinical study reports, in addition to information on reports of trials that were considered “pivotal” (that is, first or second line evidence to regulators in support of the registration application). Open label and post-marketing studies were excluded.

We included trials in previously healthy children and adults, excluding those with illnesses such as malignancy or HIV infection. We included only trials on those exposed to naturally occurring influenza with or without symptoms. We targeted the intention to treat (ITT) and safety populations, firstly because prior reviews from our group discovered compelling evidence that the ITT influenza infected (ITTI) were not balanced between treatment groups in oseltamivir (another neuraminidase inhibitor) trials, and secondly because estimates from ITT populations will be more generalisable to practice where routine testing for influenza is not common and often not available. We also compared treatment effects for time to first alleviation in adults between subgroups with and without influenza. We included studies in which zanamivir was administered by any route compared with placebo.

Data extraction

Two authors (IO and EAS) determined eligibility, while a third author (CJH) arbitrated. We used the seven domain Cochrane risk of bias tool[9] to appraise clinical study reports and for trial programmes. To examine the problem of reporting bias, we accessed data from clinical study reports and regulatory information. Because of the large volume of material at our disposal, we focused on identifying and analysing important details as well as constructing a coherent appraisal of large and complex trial programmes. Because of unrestricted access to full clinical study reports, we took the view that all information needed to judge risk of bias for each of the six domains of the Cochrane risk of bias should be present. We used the Cochrane risk of bias tool to appraise clinical study reports and a custom built data extraction form for recording information relevant to this appraisal (such as dates of participant recruitment and date of trial protocol).. When the information on a particular element was not available in the CSR, we judged the risk of bias as “high.” A full description of the methods used to adapt this tool and quantify biases will be published in another paper.

Our primary outcome measures for treatment studies were symptom relief, admission to hospital, and complications. For prophylaxis studies our primary outcomes were influenza (symptomatic and asymptomatic), always with laboratory confirmation, and influenza like illness (ILI), admission to hospital and complications, interruption of transmission (in its two components, reduction of viral spread from index cases and prevention of onset of influenza in contacts), and harms. The detailed lists of prespecified outcomes and protocol amendments in zanamivir treatment and prophylaxis trials are provided in appendices 3 and 4.

We made several changes to the systematic review during the process of turning the protocol into the review. We have rewritten the objectives twice, tightening up the text to bring it in line with our initial intentions and clarifying its meaning. The old objectives were: “To review clinical study reports (CSRs) identified from published and unpublished randomised controlled trials (RCTs) and relevant regulatory data on

effectiveness and harms of NIs for influenza in all age groups" and "To review published and unpublished clinical study reports and other relevant regulatory data on effectiveness and harms of NIs for influenza in all age groups (and compare them with our published review)." We changed the emphasis of the objectives on unpublished study reports as we had decided from the start to concentrate on regulatory information. Similarly, comparison of published versus unpublished data is important and worthwhile, but the original objective possibly misled readers as to its importance in our work. We had always conceptualised it as a low priority task we could carry out only if we had time after our review of unpublished data. We have also avoided using acronyms, which we thought cumbersome and confusing to the reader.

Our initial intention was to review clinical study reports and regulatory comments making up what we have subsequently called "regulatory information." The edits do not reflect a change in intent but our slowly evolving understanding of the problems we faced and our solutions to deal with these problems. While the review was underway we became aware of several other biases that we judged and recorded. The extraction sheet for the risk of bias was finalised before, but inadvertently not mentioned, in our protocol amendments of May 2013. A post hoc analysis was also undertaken by mode of pneumonia diagnosis: in two trial of zanamivir treatment in adults, pneumonia was based on a stricter definition of x ray confirmation and in nine trials pneumonia was based on a self reported investigator mediated unverified outcome (self reported cases of pneumonia that were not verified by x ray but were accepted and reported as pneumonia by the study investigators).

Because of the sizeable quantity of available data, we divided the extraction, appraisal, and analysis of the data into a two stage exercise. In stage 1 we assessed the reliability and completeness of the clinical study reports. We included data in stage 2 of the review—full analysis following standard Cochrane methods—only if the study reports satisfied the following three criteria:

- Completeness—Clinical study reports/unpublished reports that included identifiable CONSORT statement specified methods to enable replication of the study. Identifiable CONSORT statement specified results (primary outcomes, tables, appendices) had to be available
- Internal consistency—All parts (for example, denominators) of the same clinical study reports/unpublished reports were consistent. Access to full clinical study reports allowed us to follow consistency across chapters and appendices, creating a need for far more interaction with the text. The parts of a clinical study report we checked for consistency included the core report, the pre-study documents, study methods, individual subject listings of demographic and efficacy data, and individual listings of safety data, as well as the statistical analysis plan and the serious adverse events
- External consistency—Consistency of data as reported in regulatory documents, other versions of the same clinical study reports/unpublished reports, and other references were established by cross checking.

We developed a comprehensive strategy for dealing with data which we knew were missing at the trial level—that is, unpublished trials (see appendix 2)—and unreliable published records that are a concentrated summary of clinical study reports.

Data synthesis

Relative risks and risk differences were used to estimate treatment effects for binary data and mean differences for time to first alleviation of symptoms. To estimate treatment effects we first calculated the risk ratios (RRs) and used the average (mean) control event rate and the pooled RRs reported in the figures to calculate the risk differences (RD). For consistency we adopted this method for both the summary of finding tables and for the RDs reported in the text. For the analysis we chose to report the RRs as they are more consistent across the studies, and we have reported the heterogeneity for the pooled RR. We used τ^2 (inverse variance method) and I^2 statistic to estimate variance between studies as measures of the level of heterogeneity and χ^2 to test for heterogeneity. When possible, high estimates of heterogeneity were investigated with subgroup analysis. We used the χ^2 test for subgroup differences provided in Revman.

For analysis of harms we were limited by the frequency of occurrence of some adverse events. We therefore meta-analysed all serious adverse events; all adverse events leading to study withdrawal; and all withdrawals and all adverse events within a clinical study report's defined body system. We also identified a small number of common adverse events (incidence >2%) from the FDA label that we compared separately. There were too few events to meta-analyse deaths, serious adverse events by body system, and any events that had overall incidence less than 0.5%. We did not meta-analyse outcomes with fewer than 10 events in total. When applicable we conducted analyses separately for periods on and off treatment.

We used Revman version 5.2 for the analyses and the forest plots. We used the random effects approach of DerSimonian and Laird based on mean differences for analysis of time to first alleviation of symptoms. For all other outcomes we used the random effects approach for binary data of DerSimonian and Laird, where τ^2 was estimated with the inverse variance method. Additional analyses were reported as "post-protocol."

We also planned to use the fixed effect method of Mantel and Haenszel as a sensitivity analysis to supplement our primary analyses using the random effects method of DerSimonian and Laird. Random effects meta-analysis is known to be overly conservative with sparse data. Hence we planned to conduct sensitivity analysis using Peto's method where we had sparse data and borderline significant results. However, there were no endpoints that met these criteria for zanamivir.

The review protocol was first published in 2011 and subsequent amendments were published in 2012 and in the current review (see feedback/review amendments 16 May 2013).[6]

Results

We identified 30 eligible trials from our searches (fig 1⇓). Of these, one was excluded because it was open label design and another because it was not a prophylactic or treatment study. This left 28 trials reported in 27 CSRs for inclusion (references in appendix 5): six compared zanamivir with usual care in the prevention of influenza A and B among populations exposed to a local epidemic, two for the prevention of transmission of influenza among households, and 20 trials of the treatment of influenza A and B (tables 1 and 2).⇓⇓ The 28 trials included a total of 14 628 participants (7678 in treatment trials and 6950 in prophylaxis trials), whose ages ranged from 5 to over 65.

Two trials were excluded from the meta-analysis: NAIA3003 compared zanamivir with usual care (another antiviral) and not placebo for treatment of influenza, and the report for NAI30020

was only a synopsis. We finally included 26 zanamivir trials in the meta-analysis: 14 on treatment in adults (JNAI-01; JNAI-04; JNAI-07, NAI30008; NAI30011; NAI30012; NAI30015; NAIA/B2008; NAIA2005; NAIA3002; NAIB2005; NAIB2007; NAIB3001; NAIB3002), two on treatment in children (NAI30009; NAI30028), and 10 trials on prophylaxis (167-101; NAI30034; NAIA/B2009; NAIA2006; NAIA3004; NAIA3005; NAIB2006; PE-01; NAI30010; NAI30031).

There were variations in the reporting quality of the included studies (fig 2⇓). Only one study showed adequate randomisation technique, while 25 (89%) showed adequate allocation concealment. Adequate blinding of participants and personnel was reported in only two studies, while 24 (86%) showed adequate blinding of outcome assessors. In addition, almost half of the trials had selective reporting and reported outcomes not specified in the protocol provided. Some trials were under recruited and some used different relief drugs within the same trial across different centres. We also noted several other items that were not included in all full clinical study reports that could introduce other biases:

- Certificates of analysis for the intervention/placebo preparations
- Patient enrolment dates explicitly reported (only trial inception and cessation dates are given; in zanamivir trials these are partially redacted)
- Explicitly reported date of trial unblinding. We often noted the statement “the database was authorised on xxxx” to identify the unblinding date but an explicit date is important to report. In some cases, the date of unblinding was reported but the actual date within the month was redacted
- Authorship and accountability for the writing of the clinical study reports
- Statistical analysis plans in some cases
- Patient consent forms (missing from most zanamivir trials)
- Patient information forms (missing from most zanamivir trials)
- List of randomisation codes (variably included)
- Case report form templates in zanamivir trials do not allow for determining who completes the form (patient or clinician)
- Core data sheet.

A further explanation of these other biases can be found in appendix 6.

Time to alleviation of symptoms

Zanamivir reduced time to first alleviation of symptoms in adults by 0.60 days (95% confidence interval 0.39 to 0.81 days, $P<0.001$, $I^2=9\%$), which equates to an average 14.4 hours’ reduction, or a 10% reduction in the mean duration of symptoms from 6.6 days to 6.0 days (table 3⇓; fig 3 in appendix 7). The effect in children was not significant (mean difference −1.08 days, 95% confidence interval −2.32 to 0.15; fig 4 in appendix 7). A test for subgroup difference between adults and children shows no evidence of a difference (χ^2 0.58, P=0.45) with the overall effect being 0.66 days’ reduction in time to first alleviation of symptoms (95% confidence interval 0.44 to 0.87 days, $I^2=20\%$).

In eight zanamivir trials, time to first alleviation of symptoms was shorter in all participants when any relief drugs were allowed compared with no use, with the difference in median time to first alleviation as large as 2.5 days (NAI30011, NAI30012) (table 4).⇓

In subgroup analysis there was no significant difference in treatment effects by infection status for time to first alleviation of symptoms in adults (P=0.53; fig 5 in appendix 7). The treatment effect for patients with influenza was 0.67 days (95% confidence interval 0.35 to 0.99 days, $I^2=17\%$) compared with 0.52 days (0.18 to 0.86 days, $I^2=0\%$) for patients without influenza (see fig 5 in appendix 7).

Analysis of influenza outcomes in prophylaxis studies

Zanamivir significantly reduced the risk of symptomatic influenza in prophylaxis of individuals (RR 0.39, 95% confidence interval 0.22 to 0.70, $I^2=45\%$; RD 1.98%, 0.98% to 2.54%; number needed to treat to benefit (NNTB) 51, 40 to 103; table 5⇓,fig 6 in appendix 7) as well as in postexposure prophylaxis of households (RR 0.33, 0.18 to 0.58, $I^2=40\%$; RD 14.84%, 12.18% to 16.55%, NNTB 7, 6 to 9; fig 7 in appendix 7). However, the heterogeneity of this effect was moderate, and, apart from one study (NAI30034), the sample sizes were small. In contrast, zanamivir did not significantly affect the risk of asymptomatic influenza in prophylaxis of individuals (RR 0.97, 0.76 to 1.24, $I^2=0\%$; fig 8 in appendix 7), nor in postexposure in households (0.88, 0.65 to 1.20, $I^2=0\%$; fig 9 in appendix 7).

Analysis of admissions to hospital

Data on admissions for the zanamivir studies were not reported.

Analysis of complications

In two trials of zanamivir in adults (NAI30012; NAI30015) the reporting of pneumonia was based on a stricter definition of x ray confirmation, and there was no significant effect (RR 1.02, 95 % confidence interval 0.35 to 3.02, $I^2=39\%$; fig 10 in appendix 7). In nine zanamivir trials (NAI30008, NAI30010, NAI30011, NAIA/B2008, NAIA2005, NAIA3002, NAIB2007, NAIB3001, NAIB3002) pneumonia was a self reported investigator mediated unverified outcome. Overall, there was no significant effect of zanamivir on mixed verified and unverified pneumonia in adult treatment (0.90, 0.58 to 1.40, $I^2=0\%$; fig 11 in appendix 7). Figure 12 in appendix 7 shows that in prophylaxis trials, zanamivir reduced the risk of self reported investigator mediated unverified pneumonia in adults (RR 0.30, 0.11 to 0.80, $I^2=0\%$; RD 0.32%, 0.09% to 0.41%; NNTB 311, 244 to 1086).

Treatment with zanamivir reduced the risk of bronchitis in adults (RR 0.75, 0.61 to 0.91, $I^2=3\%$; RD 1.80%, 0.65% to 2.80%; NNTB 56, 36 to 155; fig 13 in appendix 7), but there was no evidence that zanamivir reduced the risk of other complications including otitis media (RR 0.81, 0.54 to 1.20, $I^2=0\%$; fig 14 in appendix 7), and sinusitis (1.12, 0.84 to 1.48, $I^2=30\%$; fig 15 in appendix 7).

There was no significant effect of zanamivir in reducing the risk of any complication classified as serious or that led to study withdrawal in adult treatment (RR 1.10, 0.46 to 2.63, $I^2=0\%$; fig 16 in appendix 7) and in prophylaxis (1.09, 0.36 to 3.26, $I^2=0\%$; fig 17 in appendix 7). This outcome could not be assessed in children because of an insufficient number of events.

Harms

In adult treatment trials we found no evidence that zanamivir was associated with an increased risk of reported adverse events. Nausea and vomiting was less frequent in the zanamivir

treatment arm, although there was considerable heterogeneity (RR 0.60, 0.39 to 0.94, P=0.02, I^2=50%; RD 1.63%, 0.24% to 2.48%; NNTB 62, 41 to 411; fig 18 in appendix 7). There was no evidence of these effects continuing into the off-treatment phase. Data on harms for trials involving children were sparse, and there was no increased risk of adverse events for children randomised to zanamivir.

In harms analysis in prophylaxis trials there was no increased risk of adverse events from zanamivir during the on-treatment phase. Eight deaths occurred, two were reported as due to influenza A pneumonia (one participant was taking inhaled rimantadine plus placebo and the other was taking zanamivir).

We noted in one zanamivir trial NAI30031 that according to the protocol, participants receiving antibiotics for bacterial respiratory tract infection should have been excluded, but in this did not happen. The placebo for zanamivir trials contained lactose powder, which can potentially cause bronchospasm, but certificates of analysis for the intervention/placebo preparations were not available except for one trial. Hence we were not able to confirm the exact contents of the placebo used in most of the trials and the risk of bronchospasm after exposure to zanamivir remains difficult to quantify.

Discussion

Principal findings

Zanamivir can relieve symptoms in people with influenza, mainly for self reported outcomes. Our analyses also suggest that zanamivir makes people with influenza-like illness and self reported investigator mediated unverified pneumonia feel better by shortening the duration of symptoms and reducing the frequency of symptoms such as cough. Our results confirm previous estimates of the benefit of zanamivir on symptoms. This reduction is small and similar to that seen with oseltamivir,[10] which equates to just over a half day reduction of symptoms in adults, with no significant effect in children. However, additional analyses suggest that the effect on symptoms might in part be explained by the use of relief drugs, as symptoms were not better in the treatment arm when compared with symptoms in people in the placebo group taking relief drugs. These effects seemed similar for patients with and without influenza. This finding was consistent with findings from our sister review of oseltamivir and suggests the possibility of a non-virus specific mode of action of zanamivir. We plan to publish a full report of these analyses in a separate paper.

In terms of alleviation of symptoms, this endpoint is not the same as complete cessation of symptoms. This point was noted by the US regulatory authorities: in a letter, dated 13 March 2000, the FDA's director of advertising and labelling policy raised concerns over the instability of the symptom endpoint: "Symptom relief may not be sustained since the pivotal trial showed some fluctuation after the primary endpoint was reached in both treatment groups."[11] The results of the symptom analyses should also be interpreted with caution as endpoints were changed. As an example, in trial NAIA30028, the primary endpoint was originally the time to alleviation of the main signs and symptoms of influenza, but this was later adjusted to the time to alleviation of fever. Our analysis of relief drugs was hampered because a number of trials, but not all, reported data on alleviation of symptoms with and without relief drugs. Our Cochrane review presents further secondary analyses, which aim to better understand this endpoint.

In zanamivir prophylaxis studies, symptomatic influenza was reduced by only a small amount: 54 people need to be treated to prevent one person from having symptoms of influenza infection; importantly reductions in asymptomatic influenza cases were not significant. While asymptomatic individuals can shed virus, a recent systematic review concluded that more studies are required to examine the transmissibility of influenza in this group of individuals.[12] While it might be debatable whether or not asymptomatic individuals spread influenza, the current results do not provide evidence of an effect of prophylaxis in asymptomatic individuals and on reducing the risk of transmission. In addition, while there was a greater effect in households treated prophylactically, the evidence to support this was based on data from only two small studies involving 824 participants. There was a small effect of prophylaxis on self reported pneumonia in adults, but not in children and no effects on bronchitis or otitis media in adults or children. The evidence, therefore, does not indicate that the use of zanamivir is effective in the postexposure prophylaxis of influenza.

None of the previous reviews were able to clarify how diagnostic endpoints were verified (for instance, pneumonia) and delineated self reported outcomes from those that are verified by objective measures.[1 2 8 13 14] To our knowledge, no trial or systematic review has reported on the use of relief drugs and analysed this important confounder. We have provided the most comprehensive and up to date analysis of harms and we can also confirm that data on admissions in the zanamivir studies were not reported. Further to this we have reported several biases that are not seen in journal publications but are relevant to the assessment of clinical study reports. In addition, our results do not provide evidence of an effect on asymptomatic influenza and on reducing the risk transmission.

To our knowledge, this is the first time a systematic review has been based on all relevant full clinical study reports of a class of drugs integrated by regulatory comments. Also for the first time, all clinical study reports of trials in a manufacturer's programme (regardless of their relevance to the review) are available to readers without any restriction (apart from minimal redactions to further protect anonymity). Access to evidence has proved crucial in determining the effects of zanamivir, and early decision making on regulatory approval has been hampered by a lack of access to the trial data. In February 1999, the US Food and Drug Administration (FDA) Antiviral Drug Advisory Committee voted (by 13 to 4) that zanamivir did not meet conditions for approval. However, by July 1999 the FDA had approved zanamivir; at the time only one clinical trial had been published showing significant evidence of benefit. Through a freedom of information request, Public Citizen (a customer advocacy rights group) obtained the FDA's reviews of zanamivir, which showed that only a further two unpublished studies had been submitted to the FDA.[15] Yet in April 2009, a letter from the FDA authorised the emergency use of zanamivir inhalation powder for treatment and prophylaxis of influenza, despite no evidence of its effectiveness.[16] Early evidence substantially overplayed the benefits of zanamivir, leading to ongoing stockpiling; initial editorials by key opinion leaders in this journal[17] and others[18] overestimated the benefits of the drug, particularly in primary care populations. It is also worth noting that to date there has been no publically funded trial of zanamivir, which given that we know manufactured funded trials overstate treatment effects is somewhat puzzling, given the extensive use and stockpiling of this drug.

There are several reasons why we believe the prophylactic effects of zanamivir might not be clinically meaningful. Firstly, according to modelling studies, for prophylactic treatment to be effective 80% of the population require at least eight weeks of treatment (which has never been trialled).[19] Secondly, there

is an assumption that the relative risk reduction, only observed in low risk populations, transfers directly to populations at higher risk; models that aim to contain pandemic influenza, with antiviral agents, therefore assume a high absolute treatment effect of 31%, some 15-fold higher than the absolute effect of 2% we observed across prophylaxis trials.[19] Thirdly, a high proportion of people, at least 67%, require recognisable influenza symptoms, and the treatment has to be effective against both asymptomatic and symptomatic infections (which it is not), as asymptomatic infections are assumed to be 50% as infectious as symptomatic infections.[19] Fourthly, because the influenza season typically lasts four to five months, any secondary strategy, such as vaccination, would have to be widely available at the end of an eight week treatment period, otherwise individuals at the end of prophylaxis would revert back to the same risk of infection they were at the outset. Finally, a full understanding of the effect of the treatment in prophylaxis is unknown because symptomatic influenza-like illness without laboratory confirmation was fully reported in only one study. This study (NAI30034) showed no difference in proportion of patients with symptomatic influenza-like illness (with or without lab confirmation) (RR 0.90, 95% confidence interval 0.73 to 1.11).

Overall the two drugs, zanamivir and oseltamivir, have similar benefit profiles but quite different adverse effect profiles. Zanamivir is administered as a powder inhaled twice daily. After inhalation, the drug is concentrated in the respiratory tract, with 10-20% of the active compound reaching the lungs; the rest is deposited in the oropharynx. Only 5-15% of the inhaled dose is absorbed and excreted in the urine, with a bioavailability of 2%.[18 The small amount of the zanamivir drug that is absorbed could explain the lower adverse effect profile compared with the orally administered drug oseltamivir. In terms of zanamivir's apparent effect in reducing nausea, this effect is tempered by the high heterogeneity and could be partially explained by the presence of lactose in the placebo capsules. The lack of certificates of analysis prevented us from examining whether the amount of lactose was sufficient to increase nausea in the placebo arm.

Of note, in the clinical study report NAI30012, the Protocol Amendment 11 (dated 24 Nov 2000) applied to all sites and clarified exclusion criteria to ensure patients with severe persistent asthma were no longer recruited into the study. The reason behind this amendment is cited in the body of clinical study report NAI30012: "There have been spontaneous adverse event reports of patients being treated with zanamivir who have experienced bronchospasm and/or decline in respiratory function which may be acute. Bronchospasm and dyspnoea have therefore been included as undesirable effects in the core safety information (CSI) for zanamivir. In addition, the CSI contains a warning that there have been very rare reports of patients being treated for influenza who have experienced bronchospasm and/or a decline in respiratory function after the use of zanamivir, some of whom did not have any previous history of respiratory disease." In a phase I study of zanamivir, bronchospasm was reported in one out of 13 patients without influenza with mild or moderate asthma.[20] In a recent open label study of 400 patients, bronchospasm was also reported in a women aged 38 who had no history of underlying respiratory disease; the symptoms subsided when she stopped taking the drug.[21]

The zanamivir trials were almost all performed in high income countries, mostly in North America, Western European countries and Japan, with only a small proportion recruited from middle income countries. All trials excluded pregnant women and women at risk of pregnancy. Most trials were performed on adults who were healthy, were not elderly, and were not at high risk of complications of influenza. Therefore the generalisability of these trials to populations in low or middle income settings or to individuals most at risk of complications of influenza is low.

Strengths and weaknesses

Although we expected clinical study reports to provide the most comprehensive account possible, we encountered difficulties in identifying all the relevant information: incomplete reporting in some of the CSRs (such as missing certificates of analysis) might have influenced our decision making about the risk of bias. Knowledge of new potential biases accumulated during the review process. It is therefore possible that there were inconsistencies over time in the reviewers' approach to scrutinising the trial documents. However, we tried to deal with this by discussing our findings as we went along and by having a second reviewer independently produce the risk of bias assessment. In addition, a second independent reviewer checked the characteristics of included studies, timeline checks, and missing information sections.

In addition, we used the Cochrane seven domain "risk of bias" instrument. The availability of partial or complete clinical study reports decreased the uncertainty and allowed us to make definitive judgments. Previous unclear risk of bias therefore became certainty of presence or absence of bias. However, there is still some uncertainty as to whether the complete study reports represent an exhaustive and coherent source of trial narrative and data, which would undermine this judgment.

Implications for practice and research

There is no plausible evidence that zanamivir has an effect on pneumonia, even when a chest x ray supported the diagnosis, nor did it affect otitis media or sinusitis in adults, and there was no effect on clinically important outcomes in children such as otitis media. It did affect bronchitis, which probably reflects its symptom relieving effect. However, in the absence of a clear definition of bronchitis in the trials, zanamivir is no more effective in relieving symptoms than commonly used over the counter symptomatic drugs (such as paracetamol or NSAIDs). Based on the findings of this review, we do not believe further clinical trials of zanamivir are warranted, given that the symptom relieving and symptomatic influenza preventing effects are established and the effects on clinical complications are likely to be trivial. Efforts should focus on identifying individuals at highest risk of complication and targeting them with early diagnosis and effective preventive measures. Our review also calls into question commonly used methods for conducting systematic reviews that fail to consider the entire trial programme and include only published trials. Such reviews inevitably risk providing a biased assessment of an intervention's true benefits and harms.

Conclusions

Our findings confirm that zanamivir reduces the time to symptomatic improvement in adults and confirm its prophylactic effects in those with symptomatic influenza. The effect on time to symptomatic improvement is small, about half a day on average, and it seems possible that the effects of relief drugs might be greater than any effect of the zanamivir. We found no evidence that zanamivir reduces the risk of complications of influenza, particularly pneumonia, or the risk of admission to hospital or death. Its use was not associated with a significant

increase risk of harms. Our findings do not support the mode of action of zanamivir proposed by the manufacturers.

We thank Kamal Mahtani, Jeremy Howick, Peter Doshi, Rokuro Hama, Chris Del Mar, Liz Dooley, Peter Collignon, and Toby Lasserson for help with data extraction, assessment of methods, expert advice, and proof reading of the corresponding Cochrane systematic review. We also thank Ruth Davis for providing logistic support. The National Institute of Health Research (NIHR) School for Primary Care Research (SPCR) provides financial support for CJH and funding for an investigators' meeting in Oxford (UK). This paper is based on Cochrane Review A159, which should be published simultaneously in the Cochrane Database of Systematic Reviews.

Contributors: TJ, CJH, MJ, EAS, and IO were authors of the separate relevant Cochrane review in healthy adults. TJ, MJ, and CJH contributed to the writing of the protocol for this review and devised the approach strategies to the data sources. TJ reviewed regulatory material, TJ, CJH, MJ applied inclusion criteria. All authors extracted data and appraised bias. CJH, IO, and EAS checked the data. MJ carried out the statistical analyses. IO and CJH prepared the final text, and all authors contributed to the final draft. CJH is guarantor.

Funding: This project was funded by the NIHR Health Technology Assessment programme and will be published in full in the Health Technology Assessment journal series (see www.nets.nihr.ac.uk/projects/hta/108001 for more details). The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Department of Health. The study sponsor had no role in study design, the collection, analysis and interpretation of data, the writing of the article and the decision to submit it for publication. All the authors have no ties to the manufacturer or the sponsor (apart from those disclosed) and had access to all parts of the anonymised clinical study report from the zanamivir evidence programme.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare that all review authors have applied for and received competitive research grants. TJ, PD, MJ and CJH are co-recipients of the NIHR grant to carry out this review. TJ receives royalties from his books published by Blackwells and Il Pensiero Scientifico Editore, Rome. TJ is occasionally interviewed by market research companies for anonymous interviews about phase I or II pharmaceutical products. In 2011-13, TJ acted as an expert witness in a litigation case related to oseltamivir phosphate; Tamiflu, and in a labour case on influenza vaccines in healthcare workers in Canada. In 1997-99, TJ acted as consultant for Roche, in 2001-02 for GSK, and in 2003 for Sanofi-Synthelabo for pleconaril (an anti-rhinoviral that did not get approval from FDA). TJ is a consultant for IMS Health. TJ, MJ, CJH, and Peter Doshi are co-recipients of a UK National Institute for Health Research grant (HTA-10/80/01 Update and amalgamation of two Cochrane reviews: neuraminidase inhibitors for preventing and treating influenza in healthy adults and children: www.hta.ac.uk/2352). CJH receives payment for running educational courses at the University of Oxford and University of Oxford ISIS consulting services for external teaching and training. He also receives royalties for books (Evidence Based Toolkit series by Blackwell, BMJ Books).

Ethical approval: Not required.

Transparency: The lead author (the manuscript's guarantor) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Data sharing: Data will shortly be available through the Dryad repository (www.datadryad.org).

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Accepted: 04 April 2014

Cite this as: *BMJ* 2014;348:g2547

What is already known on this topic

Neuraminidase inhibitors are used for the treatment and prophylaxis of influenza.

The evidence for their effectiveness in preventing complications of influenza is sparse, and information regarding their adverse events is lacking

Previous systematic reviews and health policy decisions have been based only on published trial data

What this study adds

This is the first systematic review that evaluates the effectiveness and safety of zanamivir using the evidence from unpublished clinical study reports and relevant regulatory comments (about 15 000 pages)

We found no evidence that zanamivir reduces the risk of complications of influenza, nor the risk of admission to hospital or death

The results show no association between zanamivir and a reduction in asymptomatic influenza and subsequent risk of transmission

Tables

Table Table| **1 Characteristics of trials of zanamivir for treatment of influenza***

				Recruited/confirmed			
Trial (drug)	**Inclusion criteria**	**Exclusion criteria**	**Age**	**Intervention**	**Control**	**Outcomes reported**	**Duration of follow-up (days)**
JNAI-01, 1995, Japan	Influenza-like illness of ≤36 hr duration	Suspected bacterial infection, drug abuse, unstable chronic illness	16-65	77/34	39/22	Time to alleviation of symptoms	28
JNAI-04, 1996/6, Japan	Influenza-like illness of ≤36 hr duration	Suspected bacterial infection, drug abuse, unstable chronic illness	≥16	32/16	16/6	Time to alleviation of symptoms	22
JNAI-07, 1996/9, Japan	Influenza-like illness of ≤36 hr duration	Suspected bacterial infection, drug abuse, unstable chronic illness, use of antivirals	≥16	220/153	113/72	Time to alleviation of symptoms	22
NAI30008, 2000, US, Canada, 10 European countries, Australia, Chile, South Africa	Influenza-like illness + temp ≥37.8°C; history of asthma or COPD	Pregnancy, hypersensitivity, suspected bacterial infection at screening	≥12	262/160	263/153	Time to alleviation of symptoms, incidence of complications, use of antibiotics	28
NAI30009[w2], 1998-9, US, Canada, Europe, Israel	Influenza-like illness of ≤36 hr duration + temp ≥37.8°C + no evidence of bacterial infection	Immunosuppressed, cystic fibrosis, underlying condition that would prevent data collection	5-12	224/164	247/182	Time to alleviation of symptoms, pyrexia, return to normal activity. Incidence of complications. Use of antibiotics	28
NAI30011, 1999-2000, USA	Influenza-like illness + temp ≥37.8°C (37.2°C for patients >65 years	Pregnant, hypersensitivity, immunocompromised	≥18	229/104	237/107	Time to alleviation of symptoms, time absent from work, time to perception of influenza symptom improvement	21
NAI30012, 1999-2001, US, Canada, 15 European countries, Australia, Chile, South Africa	Influenza-like illness + temp ≥37.8°C	Patients on antibiotics for RTI, severe persistent asthma, immunocompromise	>65	191/120	167/114	The time-to-alleviation of symptoms, incidence of complications, use of antibiotics	29 (telephone contact on day 56)
NAI30015, 2000-2001, Finland	Conscripts of the Finnish Army, living in residential units; influenza-like illness + temp ≥37.8°C	Hypersensitivity, use of antibiotics for suspected RTI, use of influenza antiviral drugs	17-29	293/222	295/213	The time-to-alleviation of symptoms, incidence of complications, use of antibiotics	29
NAI30020, 1999-2001, Germany, UK	Influenza-like illness + temp ≥37.8°C	Pregnant, suspected bacterial infection	>18	223/189	106/97	Time to alleviation of symptoms, pyrexia, return to normal activity. Incidence of complications	6 (telephone contact on day 14)
NAI30028[w1]†, 2000-1, Germany	Influenza-like illness of <48 hr duration + temp ≥37.8°C + no evidence of bacterial infection. Rapid influenza test positive	Not reported	5-12	176/176	90/90	Time to alleviation of symptoms, return to school, incidence of complications	5

Table (continued)

Trial (drug)	Inclusion criteria	Exclusion criteria	Age	Recruited/confirmed Intervention	Recruited/confirmed Control	Outcomes reported	Duration of follow-up (days)
NAIA/B2008, 1995/6, 11 European countries, USA, Canada	Patients with a duration of influenza-like illness for ≤48 hrs	Pregnancy, chronic illness, drug abuse, hypersensitivity, use of antivirals	≥13	834/482	422/240	Time to alleviation of symptoms, return to normal activity, incidence of complications	21
NAIA2005, 1994/5, North America	Influenza-like illness of <48 hr duration + temp ≥37.8°C	Suspected bacterial infection, use of antibiotics, unstable chronic illness, influenza immunization, at risk of developing complications, drug abuse	≥13	139/71	81/40	Time to alleviation of symptoms, return to normal activity	21
NAIA3002, 1997/8, North America	Influenza-like illness + temp ≥37.8°C (37.2°C for patients >65 years	Pregnancy, chronic illness, drug abuse, hypersensitivity, use of antivirals, immunosuppression	≥12	412/312	365/257	Time to alleviation of symptoms, return to normal activity	28
NAIB2005, 1994/5, 10 European countries	Influenza-like illness of <48 hr duration	Suspected bacterial infection, influenza immunization, unstable chronic illness, at risk of developing influenza, immunosuppression, pregnancy	>18	134/102	63/49	Time to alleviation of symptoms, return to normal activity	28
†NAIB2007, 1995/6, Australia, South Africa, New Zealand	Laboratory confirmed influenza of ≤48 hrs	Asthma, suspected bacterial infection, pregnancy, chronic illness, use of antivirals, drug abuse	≥13; ≥16 or ≥18	371/230	183/118	Time to alleviation of symptoms, return to normal activity	28
NAIB3001, 1997, Australia, South Africa, New Zealand	Influenza-like illness + temp ≥37.8°C	Suspected bacterial infection, pregnancy, hypersensitivity, chronic illness, use of antivirals, drug abuse	≥12	227/161	228/160	Time to alleviation of symptoms, return to normal activity	28
NAIB3002, 1998, 11 European countries	Influenza-like illness + temp ≥37.8°C	Suspected bacterial infection, pregnancy, hypersensitivity, chronic illness, use of antivirals, drug abuse	≥12	174/136	182/141	Time to alleviation of symptoms, return to normal activity	28

*Confirmed: participant recruited with influenza-like illness symptoms/signs who has had had a fourfold or greater influenza antibody titre rise and/or positive viral culture and/or PCR.

†Participants were aged ≥13 (aged ≥16 or ≥18 in some centres).

Table Table| **2 Characteristics of trials of zanamivir for postexposure prophylaxis of influenza***

Trial	Treatment	Intervention		Control		Outcomes	Duration of follow-up (days)
		Index cases (confirmed)	Paediatric contacts	Index cases (confirmed)	Paediatric contacts		
167-101, 1999/2000, Japan	Zanamivir 10mg or placebo once daily Placebo for 28 days. Excluded: influenza-like illness, hypersensitivity, pregnancy, drug abuse	161	—	158	—	Symptomatic, laboratory confirmed influenza during the 28 days on prophylaxis	36
NAI30010[w5], 1998-9, US, Canada, Finland, UK	Index: zanamivir 10 mg inhaled twice daily for 5 days or placebo. Contacts: zanamivir 10 mg inhaled twice daily for 10 days or placebo. Excluded: immunosuppressed	163 (78)	135	158 (79)	142	Symptomatic, laboratory confirmed influenza during the 10 days on prophylaxis	Index: up to 14 days. Contacts: 28 days
NAI30031[w6], 2000-1, 59 sites in Australasia, Europe, South Africa, US	Index: not treated. Contacts: zanamivir 10 mg inhaled twice daily for 10 days or placebo. Excluded: severe persistent asthma, already had symptomatic influenza	245 (129)	188	242 (153)	183	Symptomatic, laboratory confirmed influenza during the 10 days on prophylaxis	Index: 28 days. Contacts: 28 days
NAI30034, 2000/1, Canada, Czech Republic, France, Germany, Latvia, US	Index: zanamivir 10 mg inhaled twice daily for 28 days or placebo. Contacts: zanamivir 10 mg inhaled twice daily for 28 days or placebo. Excluded: Pregnancy, persistent asthma, drug abuse, immunosuppression	1678 (39)	—	1685 (52)	—	Symptomatic, laboratory confirmed influenza during the 28 days on prophylaxis	Index: 28 days. Contacts: 28 days
†NAIA/B2009,1995/6, 7 European countries, USA, Canada	Index and contact cases: Zanamivir (0.1mL per spray) + placebo, 2 sprays per nostril; Zanamivir 2 inhalations (5mg per inhalation) + placebo, 2 sprays per nostril twice a day; Zanamivir (5mg per inhalation) + zanamivir (16mg/mL), two intranasal sprays per nostril (0.1mL per spray) twice a day; Placebo (2 inhalations twice a day + two sprays per nostril twice a day (5 days duration). Excluded: presence of feverishness and/or fever (temperature >37.8°C) in the last 48 hours	431 (65)	—	144 (27)	—	Symptomatic, laboratory confirmed influenza during the 21 days on prophylaxis	Index: 21 days. Contacts: 21 days
†NAIA2006, 1995, Canada, USA	Index and contact cases: Zanamivir (0.1mL per spray) + placebo, 2 sprays per nostril; Zanamivir 2 inhalations (5mg per inhalation) + placebo, 2 sprays per nostril twice a day; Zanamivir (5mg per inhalation) + zanamivir (16mg/mL), two intranasal sprays per nostril (0.1mL per spray) twice a day; Placebo (2 inhalations twice a day + two sprays per nostril twice a day (5 days duration). Exclusion: influenza-like signs or symptoms, suspected bacterial infection, unstable chronic illness, use of vaccines or anti-infectives, pregnancy	49 (30)	—	15 (9)	—	Proportion of patients with laboratory confirmed influenza, proportion of patients with influenza	21 days for all cases
†NAIA3003, 1997-2000, USA	All cases: Zanamivir two inhalations (5mg per inhalation) via once a day plus one placebo tablet once a day for 14 days; or Placebo two inhalations once a day plus one rimantadine tablet (100mg) once a day for 14 days	238 (9)	—	244 (21)	—	Proportion of patients with laboratory confirmed influenza	28
†NAIA3004, 1997-2000, Lithuania, Netherlands, Israel	All cases: Zanamivir two inhalations (5mg per inhalation) once a day; or placebo two inhalations once a day for 14 days	240 (15)	—	249 (23)	—	Proportion of patients with laboratory confirmed influenza	28
NAIA3005, 1997/8, USA	All: Zanamivir (5mg per inhalation), two inhalations once a day; or placebo, two inhalations once a day for 28 days	553 (53)	—	554 (77)	—	Proportion of patients with laboratory confirmed influenza	35
NAIB2006, 1995, UK, France, Sweden	All cases: Zanamivir (5mg per inhalation), two inhalations twice a day; or placebo two inhalations twice a day for 5 days	30 (18)	—	32 (16)	—	Proportion of patients with laboratory confirmed influenza	21
PE-01, 1995/6, Japan	Orally inhaled zanamivir 10 mg + intranasally nebulized placebo, orally inhaled placebo + intranasally nebulized zanamivir, orally inhaled zanamivir 10 mg + intranasally nebulized zanamivir; or orally inhaled placebo + intranasally nebulised	33	—	11	—	Symptomatic, laboratory confirmed influenza during the 5 days on prophylaxis	Index: 36 Contact: 22 days

Table (continued)

Trial	Treatment	Intervention: Index cases (confirmed)	Intervention: Paediatric contacts	Control: Index cases (confirmed)	Control: Paediatric contacts	Outcomes	Duration of follow-up (days)
	placebo for 5 days. Exclusion: Influenza-like illness, hypersensitivity, pregnancy, drug abuse, unstable chronic disease						

*Inclusion criteria for all studies: one member with influenza-like illness in household when influenza transmission was confirmed in local area. Confirmed: participant recruited with influenza-like illness symptoms/signs who has had a fourfold or greater influenza antibody titre rise and/or positive viral culture and/or PCR.
†Prevention and/or progression of influenza A and B viral infections.

Table Table| 3 Zanamivir versus placebo for treatment of influenza in healthy adults and children

Outcomes	Illustrative comparative risks* (95% CI)		Risk ratio (95% CI)	No of participants (studies)	Risk difference (95%CI)	NNTB or NNTH (95%CI)
	Study population risk	Corresponding intervention risk				
Adults						
Time to first alleviation of symptoms (days)	—	0.6 days lower (0.81 to 0.39)	N/A	5411 (13)	N/A	N/A
Complications: Verified and unverified pneumonia	17/1000	16/1000 (10 to 24)	0.90 (0.58 to 1.40)	5876 (11)	0.17% (−0.70 to 0.73)	NNTB 574 (NNTB 137 to ∞ to NNTH 144)
Complications: Pneumonia confirmed with x ray	32/1000	33/1000 (11 to 98)	1.02 (0.35 to 3.02)	946 (2)	−0.06% (−6.56 to 2.11)	NNTH 1540 (NNTB 48 to ∞ to NNTH 16)
Complications: Bronchitis	72/1000	54/1000 (44 to 65)	0.75 (0.61 to 0.91)	6072 (12)	1.80% (0.65 to 2.80)	NNTB 56 (36 to 155)
Complications: Otitis media	21/1000	17/1000 (11 to 25)	0.81 (0.54 to 1.20)	5494 (10)	0.40% (−0.42 to 0.96)	NNTB 253 (NNTB 105 to ∞ to NNTH 240)
Complications: Sinusitis	68/1000	76/1000 (57 to 100)	1.12 (0.82 to 1.48)	6072 (12)	−0.82% (−3.27 to 1.09)	NNTH 123 (NNTB 92 to ∞ to NNTH 31)
Adverse events: nausea/vomiting in treatment (on-treatment)	41/1000	24/1000 (16 to 38)	0.6 (0.39 to 0.94)	6553 (15)	1.63% (0.24 to 2.48)	NNTB 62 (41 to 411)
Adverse events: psychiatric body system (on-treatment)	6/1000	6/1000 (3 to 13)	1.16 (0.57 to 2.38)	4732 (10)	−0.09% (−0.76 to 0.24)	NNTH 1132 (NNTB 421 to ∞ to NNTH 132)
Children						
Time to first alleviation of symptoms (days)	—	1.08 lower (2.32 lower to 0.15 higher)	N/A	723 (2)	N/A	N/A
Complications: Pneumonia	12/1000	6/1000 (1 to 28)	0.53 (0.12 to 2.38)	737 (2)	0.56% (−1.64 to 1.04)	NNTB 178 (NNTB 96 to ∞ to NNTH 62)
Complications: Bronchitis	15/1000	13/1000 (4 to 41)	0.86 (0.26 to 2.80)	737 (2)	0.21% (−2.67 to 1.10)	NNTB 482 (NNTB 92 to ∞ to NNTH 38)
Complications: Sinusitis	15/1000	13/1000 (2 to 96)	0.87 (0.12 to 6.45)	737 (2)	0.19% (−8.09 to 1.31)	NNTB 519 (NNTB 77 to ∞ to NNTH 13)
Complications: Otitis media	70/1000	70/1000 (42 to 122)	1 (0.59 to 1.72)	737 (2)	0% (−5.13 to 2.92)	NNTB ∞ (NNTB 35 to ∞ to NNTH 20)

NNTB=number needed to treat benefit; NNTH=number needed to harm.

*To estimate treatment effects we first calculated risk ratios and used average (mean) control event rate and pooled risk ratios reported in figures to calculate risk differences.

Table Table| 4 Time to alleviation* of clinically relevant symptoms of influenza-like illness (in all participants and participants with no use of relief drugs)

Study	Sample size		Median days to alleviation for all participants			Median days to alleviation and no use of relief drugs		
	Zanamivir (n)	Placebo (n)	Zanamivir	Placebo	Difference in days (P value)	Zanamivir	Placebo	Difference in days (P value)
NAI30008	262	263	6.0	7.0	1.0 (0.123)	8.0	10.0	2.0 (0.037)
NAI30009	224	247	4.5	5.0	0.5 (0.011)	5.0	6.0	1.0 (0.002)
NAI30010	76	81	4.5	5.5	1.0 (0.033)	5.5	6.75	1.25 (0.150)
NAI30011	237	229	4.50	5.00	0.50 (0.495)	7.0	7.0	0.0 (0.623)
NAI30012	191	167	6.5	7.5	1.0 (0.159)	9.0	10.0	1.0 (0.131)
NAI30015	293	295	2.17	2.67	0.5 (0.166)	3.17	3.83	0.66 (0.058)
NAIA3002	412	365	5.5	6.0	0.5 (0.228)	7.0	8.0	1.0 (0.054)
NAIB3002	174	182	5.0	7.5	2.5 (<0.001)	5.5	8.25	2.75 (<0.001)

*Alleviation defined as no fever (temperature <37.8°C), cough recorded as none or mild, and muscle/joint aches and pains, sore throat, feverishness/chills and headache recorded as absent/minimal.

Table Table| **5 Zanamivir versus placebo for prophylaxis of influenza in healthy adults and children**

Outcomes	Illustrative comparative risks* (95% CI)		Risk ratio (95% CI)	No of participants (studies)	Risk difference (95% CI)	NNTB or NNTH (95% CI)
	Study population risk	Corresponding intervention risk				
Symptoms						
Symptomatic influenza in prophylaxis of individuals	33/1000	13/1000 (7 to 23)	0.39 (0.22 to 0.70)	5275 (4)	1.98% (0.98 to 2.54)	NNTB 51 (40 to 103)
Asymptomatic influenza in prophylaxis of individuals	46/1000	44/1000 (35 to 57)	0.97 (0.76 to 1.24)	5275 (4)	0.14% (−1.10 to 1.10)	NNTB 729 (NNTB 91 to ∞ to NNTH 91)
Symptomatic influenza in household	190/1000	42/1000 (25 to 68)	0.22 (0.13 to 0.36)	824 (2)	14.84% (12.18 to 16.55)	NNTB 7 (6 to 9)
Asymptomatic influenza in post exposure prophylaxis	110/1000	97/1000 (71 to 132)	0.88 (0.65 to 1.2)	1525 (5)	1.32% (−2.20 to 3.84)	NNTB 76 (NNTB 26 to ∞ to NNTH 46)
Complications						
Unverified pneumonia	5/1000	1/1000 (1 to 4)	0.30 (0.11 to 0.80)	7662 (6)	0.32% (0.09 to 0.41)	NNTB 311 (244 to 1086)
Bronchitis	15/1000	8/1000 (3 to 18)	0.49 (0.20 to 1.19)	7662 (6)	0.79% (−0.29 to 1.24)	NNTB 127 (NNTB 81 to ∞ to NNTH 341)
Sinusitis	15/1000	14/1000 (10 to 21)	0.93 (0.64 to 1.36)	7662 (6)	0.11% (−0.55 to 0.55)	NNTB 942 (NNTB 183 to ∞ to NNTH 183)
Adverse events						
Headache (on treatment)	209/1000	201/1000 (186 to 218)	0.96 (0.89 to 1.04)	8153 (10)	0.84% (−0.84 to 2.30)	NNTB 120 (NNTB 44 to ∞ to NNTH 120)
Headache (off treatment)	36/1000	34/1000 (27 to 43)	0.95 (0.76 to 1.19)	8109 (9)	0.19% (−0.72 to 0.91)	NNTB 529 (NNTB 111 to ∞ to NNTH 140)
Cough (on treatment)	149/1000	136/1000 (122 to 150)	0.91 (0.82 to 1.01)	8153 (10)	1.34% (−0.15 to 2.68)	NNTB 75 (NNTB 38 to ∞ to NNTH 672)
Cough (off treatment)	20/1000	27/1000 (21 to 36)	1.31 (0.99 to 1.73)	8109 (9)	−0.63% (−1.48 to 0.02)	NNTH 160 (NNTB 4933 to ∞ to NNTH 68)

NNTB=number needed to treat benefit; NNTH=number needed to treat harm.

*To estimate treatment effects we first calculated risk ratios and used average (mean) control event rate and pooled risk ratios reported in figures to calculate risk differences. There were no data for prophylaxis trials in children.

Figures

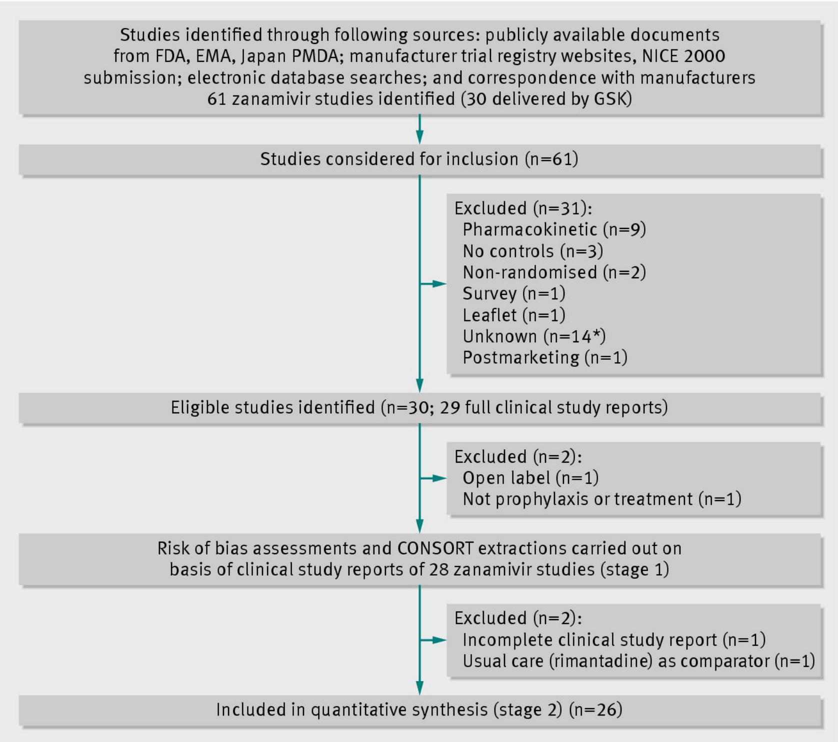

Fig 1 Flow diagram describing number of studies identified, inclusion, exclusion and progression from identification to stage 1 to stage 2 of review. Because of absence of trial programmes for zanamivir listing all sponsored trials completed or underway, we had to rely on various sources for reconstruction of trial programmes and retrieval of relevant clinical study reports

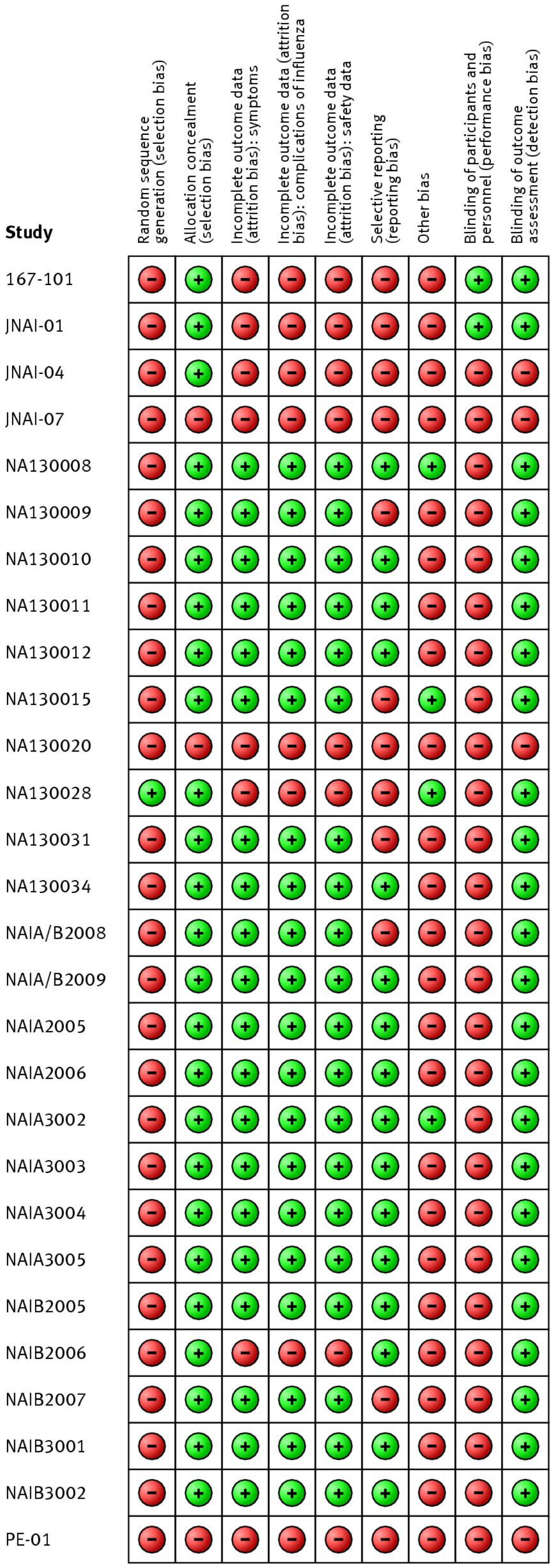

Fig 2 Variation in reporting quality of included studies